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## after four decades

After an experience of forty years it is fitting that I should attempt an appraisal of the treatment of cervical and fundal cancer. The only two methods that result in "cures" of five years or more are either surgery or radiation therapy. For early cases of invasive cervical cancer, Stages I and II, consideration must be given to the problem of radiation sensitivity. If it can be demonstrated that the tumor, or the patient with the tumor, is resistant to radiation then radical surgery should be carried out. If the tumor or patient is sensitive, radiation is best. To distinguish between the two possibilities either histologic or smear methods are available. The problem also can be solved by observing the clinical response to radium. Unfortunately, the proper methods are not available to all, but more and more study and more and more interest in the problem will eventually unravel the situation.

For Stage III cancer, or that tumor which extends to the pelvic wall, treatment by radium and x-ray therapy comes first. If successful, the results are in the neighborhood of 30 per cent five-year arrests. If the result is obviously not good, then the

radical operation may be tried, but in most cases partial or complete exenteration will be necessary. In Stage IV cases the radiation results are very poor and total exenteration, a very formidable procedure, may give more satisfactory results. The surgery of this disease should not be attempted by a surgeon who is not familiar with the complete dissection of the pelvis. Observation of the methods in use is essential before surgery is undertaken. A poorly done surgical operation such as a simple or slightly extended total hysterectomy is not satisfactory and will lead to early recurrence of the cancer.

In cancer of the fundus or corpus of the uterus, if the tumor is all above the internal os, the accepted method of treatment is intrauterine radiation or x-ray treatment two weeks to three months before operation. Radical surgery of the type used for cervical cancer should not be attempted. The results in the hands of experts are not satisfactory enough at the present time to prove that radical surgery of the Wertheim type plus bilateral pelvic node dissection is the proper treatment.

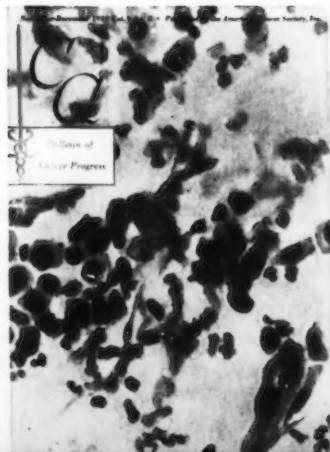
For cancer of the body, or corpus, that involves the cervix, radical surgery of the type used in cervical cancer should be the method of choice. Preoperative radiation is not advocated in this type of cancer. Radiation therapy alone is not often curative but must on occasions be used.

*for Vincent meigs*

### Cover—

Polychrome appearance of positive cervical smear stained with acridine-orange dye, in the fluorescence-microscopic method for cancer detection. Nuclear DNA has green fluorescence, while nucleolar and cytoplasmic RNA has reddish-orange fluorescence. Rapidly proliferating malignant cells have an increase in content of these acids and therefore fluoresce brilliantly.

From L. von Bertalanffy and F. D. Bertalanffy.



# NEWSLETTER

NOVEMBER-DECEMBER, 1959

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Greene's (Yale Univ. School of Medicine) investigations show that lymphosarcomas in hamsters result in death for the host, but only rarely is metastasis present (in less than 10 per cent of cases). Despite this rarity, tumor cells are widely disseminated in these animals since the transfer of blood or organs to normal hamsters is followed by the growth of typical tumor tissue in the new host. Surgical removal of the primary lymphosarcoma in the original host, however, was associated with a radical change in the incidence of metastasis. More than 60 per cent of hamsters so treated died of widespread growths. Simultaneous transfer of tumor tissue to two sites in the same animals resulted in growth of both, but no metastasis was observed. On the other hand, removal of one of the tumors was followed by metastasis, with the same incidence noted in untreated animals bearing a single growth. It appears that the presence of the primary tumor transplant exerts some influence against tumor cells circulating in the blood stream, or creates an inability in host tissue to respond to loose tumor cells.

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Survey by the United States Health Insurance Institute for 1957 showed that twice as many operations for cancer and cancer prevention were performed than in 1947. One out of seven operations was for cancer or its prevention. Removal of benign tumors, cysts and polyps as a cancer-prevention measure constituted 94 per cent of these operations.

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Wissler and Bristow (Univ. of Chicago) substantially retarded the growth of tumors in rats with no toxic effects by oral administration of beta-3-thienylalanine. When this new drug is given in conjunction with triethylene melamine, the dosage of the latter toxic drug can be reduced.

Levin (Roswell Park) recently stated that, if all cases of cancer of the breast, uterus and skin could be diagnosed and treated in the earliest stage we could probably cure two thirds of them and that if we could eliminate cancer-producing exposure to cigarette smoke we could prevent probably 70-80 per cent of lung cancer in the future. Obviously it is to the interest of those who grow tobacco, manufacture and sell cigarettes to minimize their harmful effects on health. To counteract the effect of the investment in tobacco advertising of an amount of money almost as great as the total amount spent on cancer research, some money will have to be spent using mass media to publicize what we know about the cancer hazard of cigarette smoking.

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Miller, Diamond and Craver (Memorial Center and Sloan-Kettering Institute, New York City) report that chlorambucil, an analogue of nitrogen mustard, has advantages over triethylenemelamine as an oral alkylating agent. The more consistent absorption of chlorambucil is not related to food intake, and the effect on bone marrow can be more easily controlled. The drug is as effective as other alkylating agents in treatment of Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, chronic lymphocytic leukemia and chronic myelocytic leukemia.

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Vaccine prepared from the patient's own tumor and reinforced with Freund's adjuvant seems to benefit a small, but probably significant, number of patients with advanced cancer. The Grahams, John and Ruth (Roswell Park, Buffalo), report that 55 of 101 cancer patients were alive seven months or more after vaccination--14 of these were apparently free of disease. The adjuvant used was a combination of mineral oil, an emulsifying agent (Arlacel A) and killed *Mycobacterium butyricum*.



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TOPIC: CANCER OF THE UTERUS

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ARTICLES IN *CA* ARE INDEXED IN CURRENT LIST OF MEDICAL LITERATURE AND QUARTERLY CUMULATIVE INDEX MEDICUS, AND SOME ARE ABSTRACTED IN CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, EXCERPTA MEDICA AND ABSTRACTS OF WORLD MEDICINE.

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## a glance . . .

### one-minute abstracts of the literature on cancer of the uterus

#### **Cytology in Clinic and Private Patients**

Malignant tumors of the cervix in a sub-clinical stage, having none of the typical clinical symptoms and signs, may be detected only by microscopic methods. As a screening method, the study of exfoliated cells from the cervix and vagina has demonstrated that four to six unsuspected cases of carcinoma of the uterus may be detected in each 1000 women examined. Among a group of 17,671 women studied at the University of Oklahoma Hospitals from 1948 through 1957, 71 unsuspected cases of carcinoma of the uterus were found, an incidence of 4.01 per 1000 women. In a group of 11,415 private patients, seen in the offices of six gynecologists from 1940 through 1957, 42 unsuspected carcinomas of the uterus were found, an incidence of 3.6 per 1000 women. In any screening process where an element of doubt exists as to the validity of the report, a definitive diagnostic study is indicated, but it would be desirable to eliminate the large number of "suspicious" reports which account for almost half of the biopsies done where no evidence of cancer is found. Classification of the reporting methods, so that the impression of the cytologist may be interpreted into a definite investigative procedure with a fairly clear expectation of the results, will

do much to resolve these difficulties. The American Cancer Society's recommendation for follow-up study of cytology reports, as outlined in its brochure *Cytology and Cancer of the Cervix*, is an excellent guide for the clinician.

*Hartford, W. K.: Cytology for uterine-cancer detection in clinic and private patients. Obst. & Gynec. 13:278-281, March, 1959.*

#### **Fluorescence Microscopy in Cancer Detection**

This paper presents a new evaluation of the earlier technique of fluorescence microscopy as a simple, rapid screening method in cancer detection. The acridine-orange (AO) technique described, which requires but a single organic dye, is based on the affinity of the dye for the two nucleic acids present in normal and malignant cells—desoxyribonucleic acid (DNA) found in the nucleus, and ribonucleic acid (RNA) found in the nucleolus and cytoplasm. Each normal cell contains specific amounts of DNA and RNA. Atypical and malignant cells which are rapidly proliferating appear to have an increase in these acids and show a brilliant fluorescence. Chromosome masses of the nucleus appear as green particles while the cytoplasm may reveal a red color on a blue-black background. The technique of

staining takes 12 minutes and the scanning of a normal smear requires about three minutes. This method of rapid elimination of normal smears can expedite mass screening for atypical cellular pathology. The author includes a report of findings in 1050 cases, using the AO method, and a series of color photomicrographs of smears stained by this method.

*Sussman, W.: Detection of gynecologic cancer by fluorescence microscopy. Obst. & Gynec. 13:273-277, March, 1959.*

cent) of the traced patients are presumed to be free of cancer. Two hundred and ninety-five patients (52.5 per cent) are well five years or more later. Six patients are known to have had subsequent carcinoma of the vaginal vault. One patient died in the immediate postoperative period.

*Mussey, E., and Soule, E. H.: Carcinoma in situ of the cervix; a clinical review of 842 cases. Am. J. Obst. & Gynec. 77:957-972, May, 1959.*

### Carcinoma in Situ of the Cervix

This report is a review of 842 cases of carcinoma in situ of the cervix diagnosed and treated at the Mayo Clinic from January 1, 1932 through December 31, 1957. Data are presented throughout the text and in five figures and eight tables. The ages of the patients ranged from 19 to 79 years, with a mean of 43.4 years. More than half of the patients (529) sought medical advice because of symptoms referable to systems other than the reproductive tract. One hundred and twenty-two patients had gynecologic complaints considered to be unrelated to cervical carcinoma. Abnormal vaginal bleeding or discharge was noted by 135 patients. In 56 cases a malignant lesion of the cervix had been suspected or proved prior to admission. Examination of cervical smears played a definite role in the detection of the malignant lesion in 363 cases. The data indicated that the patient's symptoms and the appearance of the cervix offered unreliable evidence of the presence of a preinvasive malignant lesion. Hysterectomy (vaginal, total abdominal, or Wertheim) was employed in 747 cases (88.7 per cent). Irradiation was employed in 40 cases. Conization was the treatment in 31 cases, cervical cautery in 12, cervical amputation in six, removal of polyp in two and no treatment in four. The potential curability of carcinoma in situ depends on the certain demonstration that the lesion is noninvasive and does not extend beyond the vaginal or cervical incision. Follow-up data for at least two years are available on 561 cases; 521 (92.9 per

### Community Uterine Cancer Detection Program

In 1947, the Academy of Medicine of Toledo and Lucas County organized a uterine cancer detection program employing vaginal smear techniques and making such screening service available to the entire female population of the Toledo area. Seven important principles are basic to the establishment of this program: (1) Enlist the aid of the pathologist—the key figure in the discipline of preparing and examining smears; (2) use cytotechnologists for screening—with six to 12 months of training they can become exceedingly proficient in initial screening of slides; (3) utilize practicing physicians—they must appreciate the value of the program, know the methods and limitations of the procedure and perform the procedure in their own offices; (4) tell the patient about the program—properly informed patients assure its growth and success; (5) provide continuity of examination—women enrolled in the program receive repeated pelvic and cytologic examinations at six to 12 month intervals throughout their lifetime; (6) preserve the doctor-patient relationship—smears and pelvic examinations are done in the physician's office and all communications with the patient are handled by the physician; (7) make the program self-supporting—financially able women pay a nominal fee; indigent patients are examined without charge. Since the program began, more than 110,000 pelvic and cytologic examinations have been performed on approximately 47,000 women. Six hundred practicing physicians have participated. Histologically proved



uterine cancer has been detected in over 430 women, 275 of whom had clinically suspected cancers, while 155 had clinically occult neoplasms detected primarily by means of smears. Women with occult uterine cancer had a five-year cure rate of 91 per cent, as compared with 38 per cent for those with suspected neoplasms.

*Burns, E. L., and Gorski, T. W.: The application of cytology to a community uterine cancer detection program; results and experiences of eleven years' operation. Am. J. Obst. & Gynec. 77:973-976, May, 1959.*

### Positive Papanicolaou Smear

When a single Papanicolaou smear of the cervix is positive, diagnostic curettage and cervical biopsy should be done. The biopsy should be of the ring or cone type, and the specimen should include all of the squamocolumnar junction of the cervical epithelium. Multiple punch biopsies of suspicious areas may be inadequate. If tissue removed from the cervix and endometrial cavity of patients beyond childbearing age is noncancerous at biopsy or cancer in situ is found, total hysterectomy is indicated. The operation may be delayed in patients of childbearing age, though continued observation is mandatory and reasons for delay must be urgent with cancer in situ. Patients with invasive cancer should have total hysterectomy, radium therapy, or a combination of radium and supervoltage x-ray therapy. In 13,250 Papanicolaou smears from patients with abnormal menstrual histories, cervical erosions and lacerations, pelvic tumors, and abnormal discharges, there were positive smears in 102 patients. Cancer was verified in 79 patients; 39 had cancer in situ, and 40 had invasive cancer.

*Swinton, N. W., and Lehman, G.: The management of patients with the positive Papanicolaou smear. S. Clin. North America 39:825-830, June, 1959.*

### Uterine Cancer Detection In Industrial Workers

Tampon smears may be used effectively for detecting uterine cancer in industrial workers. The authors believe that the procedure is as dependable as the direct smear

method, requiring the individual to be away from the job only about fifteen minutes. Among 2445 employees tested, much uterine disease and five malignant tumors were found. Each woman was instructed in technique—removing the tampon two to four hours after insertion, making the smear, and placing the slide in a jar of fixative. The smears were left in the ether-alcohol solution overnight, then dried, packed in boxes and sent to a cytology laboratory for diagnosis.

*McLean, B.; Talbot, F. G., and Jend, W., Jr.: Detection of uterine cancer in industry. A. M. A. Arch. Indust. H. 18:261-267, September, 1958.*

### Cytologic Screening in the Smaller Community

In Jackson, Michigan, during 1958, a project of mass cytologic screening of women for detection of uterine cancer was conducted through the cooperative efforts of the Michigan Department of Health, Jackson County Cancer Society, Jackson City Health Department and Jackson County Medical Society. The screening was limited to women 35 years of age and older. Smears from 1020 women were obtained and examined over a period of seven weeks. Three cases of noninvasive and one of invasive carcinoma were detected and their malignancy was confirmed by biopsy. It is believed that the results of this project represent convincing evidence to the medical profession that the screening of healthy women on a limited scale is feasible and beneficial in communities other than those having medical centers.

*Ahronheim, J. H.: Cytologic screening of healthy women in the smaller community. J. Michigan M. Soc. 58:611-613, April, 1959.*

### Treatment of Carcinoma of the Cervix

In recent years great interest has developed as to the proper method of treatment for carcinoma of the cervix. This editorial was written to point out the fact that until there is proof that cervical and parametrial lymph channels are not involved in very early cancer of the cervix,



the physician should not rely upon simple total hysterectomy as treatment of the disease. Perhaps routine lymph node dissection need not be done, but the old Wertheim operation, with removal of the paravaginal and paracervical tissues and their lymphatics and a good vaginal cuff, should be the operation of choice rather than the newer, more radical operation currently in vogue. It is much easier and less dangerous to do a simple total hysterectomy, but in all probability this operation is not sufficient. The author is distressed by the small but steady stream of patients who come to clinics with residual or recurrent cancer following inadequate surgery. Radical surgery has been of inestimable value in the understanding of cervical carcinoma. It is fortunate that it offers the means of study that may make possible reduction in the extent of operation required in certain patients. It behooves surgeons and pathologists to make use of this material to that end.

Meigs, J. V.: *Carcinoma of the cervix*. [Editorial.] *Surg., Gynec. & Obst.* 108:616-617, May, 1959.

### Colposcopy in Detection of Cervical Cancer

Colposcopy as a method of studying the cervix is well known in Europe and has paralleled the development of the cytologic method of detection of cancer. The Papanicolaou smear is specific, allows the detection of a significant proportion of cancers of the genital tract beyond visibility, but has the disadvantage of not indicating what part of the tract should be biopsied. Colposcopy is less specific but can immediately determine the right location for obtaining tissue if the lesion is on the visible cervix or vagina. The colposcope is a simple instrument consisting of a microscope of low magnification (10-20X) providing binocular vision. With the colposcope the changes seen which are associated with atypical metaplasia and carcinoma are usually found in transition zones. The changes in the first group are various types of leukoplakia; in the second group are irregular vascular changes which are a response to rapid proliferation of

tissue; in the third are irregular transition zones with irregular vascularity and a glossy, yellowish appearance; in the fourth group the changes are true erosions. The author reports 246 consecutive screening examinations, using colposcopic and cytologic techniques at the Longview State Hospital and the Cincinnati General Hospital. There were 21 cases (8.5 per cent) in which biopsy was indicated by colposcopic findings. Four additional patients had suggestive cytologic but negative colposcopic findings. Premalignant or malignant disease was found in four patients (1.6 per cent). In these, results of cytologic examination were negative in two, doubtful in one, and inadequate material was submitted in one.

Salzer, R. B.: *Colposcopy — an aid in the detection of early cancer and precancerous conditions of the cervix*. *Obst. & Gynec.* 13:451-456, April, 1959.

### Diagnosis Of Cervical Cancer In Situ

All women, regardless of age, should be examined cytologically by vaginal and cervical smears at least once a year to insure diagnosis of preinvasive cervical cancer. The cervical smear is obtained by rotating a cotton-tipped applicator in the exposed cervical canal in a clockwise direction. The swab is then unrolled in a counterclockwise direction on the slide. Fixation should be in 90 per cent alcohol. If the smear suggests cancer, the patient is recalled for additional cytologic smears, then multiple biopsy. After applying Schiller's iodine to the cervix and vaginal vault for three to five minutes, punch biopsies are obtained from at least four areas of the mucocutaneous junction. Bleeding is stopped by pressure and a tampon placed against the cervix for eight hours or more. Carcinoma in situ should be considered primarily as an endocervical disease; Schiller staining outlines extension of the lesion on the cervical portio and vaginal wall. If the punch biopsy reveals in situ cancer, the diagnosis is confirmed by semiserial examination of cold-knife cone specimens to discover invasion in areas outside the one visualized.

Kasdon, S. C.: *The laboratory, the surgeon and in situ cancer of the cervix*. *Obst. & Gynec.* 13:576-590, May, 1959.

## BIOLOGIC PREDETERMINISM

[Dr. Notkin's criticism of the term and of the concept of biologic predeterminism abstracted below, is supplemented by the following excerpts from the basic articles by the originator of the concept and term, Dr. Ian Macdonald, Associate Clinical Professor of Surgery, University of Southern California School of Medicine, Los Angeles.—Ed.]

I. The wide range of biological potential exhibited by human cancer is determined early in the preclinical phase of the disease, and probably in the actual inductive phase of neoplasia. The undue emphasis on early treatment ignores the complex biological nature of cancer, as well as the wide disparity of behavior of the disease in its variable forms and sites of origin. The behavior of a neoplasm in an individual host is an expression of a biological potential established during the inductive phase of neoplasia. The factors determining the inherent potential of a given neoplasm for growth and dissemination are probably genetic. Thus the balance of power between neoplastic and reactive influences in the host has been established in the preclinical phase of the process, and in a clinical sense this concept may be expressed as that of biological predeterminism. Rigid ideas of therapeutic measures and prognosis in terms of duration and dimension of neoplasia should be abandoned in favor of a search for more accurate criteria of the diverse biological potentialities in human cancer. Such indications of growth potential as are presently available should be applied with the intent of affording curative measures for many patients commonly regarded as presenting "late," and therefore incurable, cancer.

Macdonald, I.: *Biological predeterminism in human cancer*. Surg., Gynec. & Obst. 92:443-452, April, 1951.

II. Biologic predeterminism, rather than the time or type of surgical treatment, governs end results in gastric carcinoma. Duration of symptoms bears some relation to resectability, but curability increases with duration of symptoms in resectable cases. Present evidence indicates that, under the most ideal circumstances, less than 20 per cent of all gastric cancer is surgically curable.

Macdonald, I., and Kotin, P.: *Biologic predeterminism in gastric carcinoma as the limiting factor*

*of curability*. Surg., Gynec. & Obst. 98:148-152, February, 1954.

III. Almost 10 years ago I suggested the phrase "biologic predeterminism" as a synoptic expression for a biologic balance between host and neoplasm, established before the neoplastic process becomes clinically detectable. The outcome of the preclinical struggle for power, between a developing neoplasm and the enigmatic defensive reactions of the host, is of greater prognostic importance than the time or type of treatment. Biologic predeterminism either has been endorsed or rejected by exponents of two contrasting philosophies concerning the effectiveness of surgical therapy for cancer, but both seem to mistake predeterminism for a biologic equivalent of the doctrine of uniform predestination, or Calvinism, in theology. Some cynics have assumed that predeterminism is in agreement with those deft but dour wizards of biometry, Park and Lees, who suggest that the course of cancer of the breast is uninfluenced by treatment. On the other side of the philosophic fence protagonists of surgical superradicalism who represent "the triumph of hope over experience" employ such expressions as "a prophet of doom" in tirades decrying any recognition of the biologic facts of neoplastic life. Predeterminism emphasizes one feature of cancer therapy overlooked by those whose traditional concepts of space, time, and earliness neglect the fact that chronologically "late" cancer also may be curable. "Educational" inundation of the medical profession with outworn slogans and intellectual placebos continues unabated. Monographs on cancer of the stomach and lung keynoted as "problems in early diagnosis" were excusable even 10 years ago; today they are typical of the continuing refusal of many teachers in surgery to abandon a traditional, uniform approach to all forms of cancer. The surgeon's responsibility is the recognition of cancer at a biologically early phase, which may or may not be compatible with earliness in the temporal or dimensional sense.

Macdonald, I.: *The individual basis of biologic variability in cancer*. Surg., Gynec. & Obst. 106: 227-229, February, 1958.

This concept of biologic predeterminism, obviously too broad, does not take cognizance of the location of the lesion. It would appear that the term biologic

predeterminism is not a yardstick which can be used in evaluating the prospects of survival of a given patient. In its broader sense the term may be considered to include all the cogent factors upon which depends the fate of the patient: the grade of malignancy of the lesion; the extent of the invasion, as well as its location, before the occurrence of symptoms; and the time at which the patient becomes aware that he is suffering from something more than a passing ailment. The term biologic predeterminism would appear to be an unfortunate one because its influence is not susceptible to measurement; it connotes an almost fatalistic approach and does not appear to have any value in furthering the interests of the patient with carcinoma of the stomach. It does convey a sense of frustration, hopelessness and mysticism, and unless clarified to the point of lucidity and usefulness should be dropped. The concept that a longer history means a more favorable prognosis in a specific cancerous lesion appears to be a very confusing, though partially true, statement of fact. It is not at all illogical to believe that patients in whom carcinoma of the stomach is diagnosed, and who have a long history, may survive longer. What appears to be illogical is the implied assumption that it is therefore not harmful, and even beneficial, to delay operation. Such an assumption can be tragically harmful if, for instance, it should be finally demonstrated that the Alice-in-Wonderland concept of *The Later The Earlier* may have a very simple explanation, namely, that the long history (in cases with favorable outcome) is merely an indication that in these patients the disease may have started as gastritis or as a benign ulcer with subsequent superimposition of malignancy. Possibly a more useful concept of the life history and the significance of time in a specific instance would appear to be a multi-dimensional (time-space-intensity) concept of the lesion, where time signifies the duration of the symptoms, space denotes the area involved by the lesion, and intensity indicates the grade of malignancy. One could also include a possible fourth factor, the immunological factor suggest-

ed by Brunswick. Obviously this multi-dimensional concept could have no prognostic value preoperatively but could be helpful postoperatively. An inseparable part of the problem of the early diagnosis of gastric cancer is the ulcerated carcinoma which resembles peptic ulcer and the ostensibly simple peptic ulcer which could be a peptic ulcer with superimposed malignancy. With sufficiently early diagnosis the five-year cure rate in gastric cancer could be raised to approximately 50 per cent. Predeterminism suggests too strongly the concept of predestination and carries with it a fatalistic connotation of resignation and almost of hopelessness. If the concept is intended to signify that the recalcitrance of the lesion to all forms of therapy is predetermined on the basis of its refractoriness to all therapeutic approaches, no matter how early they are instituted, then its biological relationship and union with the host is such that it is bound to remind one of *The Man Who Came to Dinner*. Unless this concept can be used as a differentiating standard in the decision whether or not to operate, it must remain a very interesting philosophical concept. Granting the philosophical merits of the concept of biologic predeterminism, it is the author's firm belief that, should this concept become widely known and accepted, the already deeply rooted pessimism prevalent among general practitioners regarding the value of the surgical approach in cancer of the stomach will be reinforced. This is hardly desirable.

Notkin, L. J.: *The theory of biologic predeterminism: its questionable usefulness and validity as a medical tool.* [Special Article.] *Canad. M. A. J.* 81: 190-191, August 1, 1959.

[Dr. Macdonald's comments concerning Dr. Notkin's views on biologic predeterminism follow.—Ed.]

Exposure to the concept of biologic predeterminism evokes a specific reaction in many clinicians, and of particular intensity and duration among surgeons. The primary response is one of resentment of the demonstration that natural history is a more important determinant of outcome than the time, or type, of treatment. Yet

this is verified emphatically by our failure to control cancer (for an arbitrary five-year period) in more than one of every three patients, in spite of diligent effort toward "earlier" treatment made possible by the greatly increased availability of competent therapy. The emotional denial of hard biologic fact seems to prevent any real understanding of predeterminism, in favor of a conviction that the concept is entirely pessimistic, and that its originator must be a therapeutic nihilist. I have emphasized repeatedly the obverse facet of biologic predeterminism, i.e., that "late" cancer may also be curable. Equal emphasis has been placed upon the fact, ignored in Dr. Notkin's essay, that curability in some forms of cancer is indeed a function of time and space-occupation (e.g., uterus, oral cavity, skin).

Dr. Notkin chooses to attack predeterminism on the basis of a single anatomic site of cancer, and his selection could not have been more unfortunate for his purpose. [Dr. Notkin is a gastroenterologist.—Ed.] Gastric carcinoma is a neoplasm which has disseminated beyond the area of the most radical type of operation in more than 90 of 100 patients, and in 40 or more the *earliest symptom* is that due to metastasis in distant sites. In 20 per cent of patients death occurs while the primary site is still asymptomatic. In short, the *early signs or symptoms* in almost half of the patients are signals of incurability. In the remainder, both resectability and survival bear a *direct* relationship to the duration of symptoms in the Mayo Clinic series of over 6400 patients, of which the extreme comparisons follow:

Duration of Symptoms	Per cent Resectability	Per cent 5-Year Survival
0-3 months	35.8	20.8
3-4 years	53.9	38.5

In the literature of surgery statistical data usually are limited to operable (i.e., "explorable") cases, and the average surgeon is most likely to remember that 35 per cent or more of patients survive for five years after definitive resection. Seldom published are data on entire groups of *totally unselected* gastric carcinoma, as

was done by Guiss for over 2700 patients. The true net five-year survival is less than 5 per cent, made up almost exclusively of patients in whom the pattern of growth is favorable, and the primary lesion of limited local extent for long periods of time. In these patients treatment is accomplished at an *early stage of the disease*, which usually bears no relationship to earliness in a temporal sense, or even to criteria of a spatial order. As a student in the Faculty of Medicine from which Dr. Notkin and I both graduated [Notkin, McGill, 1920; Macdonald, McGill, 1928.—Ed.], I was taught that a palpable gastric cancer was an inoperable lesion. The fallacy of this dictum has been illuminated by predeterminism: the patient whose gastric neoplasm has become palpable while its host remains alive and operable often has an exophytic, bulky carcinoma limited to the gastric pouch. In others there is extension to adjacent viscera without lymph nodal or hepatic metastasis—a situation in which "extended" resection procedures are more effective than is the standard operation for the average "early" lesion. "Late" cancer may be curable, also.

Call it what you will, this sort of evidence fulfills my definition of biologic predeterminism; the biologic balance between host and neoplasm has produced a pattern of growth and spread before clinical recognition is possible, which predetermines the outcome to a greater degree than does the time or type of treatment.

I am unable to discern any effective refutation of this concept in Dr. Notkin's article, but there are certain misinterpretations which deserve correction:

(1) If I understand the title correctly, the primary approach is a misconception, for I have never thought of predeterminism as a "medical tool." The concept is of greatest importance as a philosophic basis toward a better understanding of the vagaries of the whole spectrum of disease which we designate generically as cancer, just as Notkin implies. The concept is thus *not* "obviously too broad"—it may be an inadequate intellectual exercise, but too broad it is not.

(2) Value to the clinician is twofold:

a. Emphasis upon the extreme importance of individualization of therapy for every patient.

b. Recognition of biologic variability frequently unrelated to historical duration and space-occupation.

(3) The concept is inherently fatalistic, but no more sinister than the neoplastic processes it attempts to describe. For many patients the implications are hopeful, where by traditional standards the verdict would be hopeless. The absence of "lucidity and usefulness" is due either to my failure in achieving an orderly presentation, or to Dr. Notkin's failure to read more than our article on gastric carcinoma.

(4) There has been no intent to imply that significant delay in surgical treatment is harmless, much less beneficial. We do believe that the treatment of cancer is never an emergency, and that the patient's best interests are served by thorough investigation, and physical and psychological preparation for operative procedures.

(5) We believe that the transition of peptic ulcer to carcinoma is a rare phenomenon, and that such transition never occurs in chronic gastritis.

(6) The ulcerated carcinoma radiologically indistinguishable from peptic ulcer represents usually a lesion described by Stout and others as "superficial spreading" carcinoma. As such, it is an early stage in a favorable form of gastric carcinoma, and probably an exception to the biology of the disease in general. For this reason I teach and practice the procedure of subtotal gastrectomy for gastric ulcer unhealed after six to eight weeks of a strict medical regimen, in patients past 40.

(7) The concept of a two-dimensional evaluation of the neoplastic process (time and space-occupation) is outlined in my papers to which Notkin refers; histologic structure in most forms of cancer is not a prognostic index of consistent value, while immunologic factors are still speculative.

(8) While it is true that 50 per cent of patients without lymph nodal metastasis survive for five years or more after operation, it is sheer nonsense to maintain that this figure would be achieved by "aggressive"

surgery, for, by the time that diagnosis is first possible under ideal conditions, less than 15 per cent of patients still have disease localized to the stomach.

My most vigorous dissent concerns the final paragraph of Dr. Notkin's essay [*and abstract*—Ed.], in which he implies that general practitioners should be protected from the philosophy inherent in biologic predeterminism, lest their "deeply rooted pessimism . . . regarding the value of the surgical approach in cancer of the stomach be reinforced." This sort of admonition has been tendered orally in recent years by several surgeons, and I find it as unpalatable in print as it was in conversation. The pessimism so lamented owes its deeply rooted status to nothing more than the true end results of surgical treatment for so ominous a disease. In fact, the family physician as well as the internist is more apt to have an accurate impression of the ravages of gastric cancer than is the surgeon, for the former usually will have done a preliminary screening of patients, separating those with evidence of metastases and for other reasons of inoperability, and referring only the apparently operable cases to the surgeon. In an informal canvass of more than 30 internists about ten years ago, we found only one who had a patient alive for more than three years after resection.

I prefer a belief in the propriety of free discussion of medical, scientific and technical developments, philosophic or practical, within the medical community at large in a free society. The implications of predeterminism are such that a more general knowledge of the concept among physicians should result in recognition of some "late" cases which may be operable and curable, but by traditional standards of "early" diagnosis are ineligible for reference to the surgeon. Benefits of palliative gastric resection also would be realized.

Most apparent is the fact that surgical therapy of gastric cancer can never achieve more than very minor effectiveness currently apparent. Any real contribution to its control must await totally new methods of treatment, yet to be born of research.



# Carcinoma of the Uterus

Francis M. Ingersoll, M.D., and Joe V. Meigs, M.D.

## Carcinoma In Situ

The recognition of carcinoma in situ as a precancerous condition which can progress to invasive carcinoma<sup>8, 13, 19, 28, 35</sup> is one of the exciting discoveries of our time. This fact places the gynecologist in the advantageous position of being able to prevent a serious disease—invasive carcinoma of the cervix—by the careful management of carcinoma in situ. The number of cases of carcinoma in situ has increased markedly since its earlier recognition due to the use of the Schiller test, the Papanicolaou smear and the routine biopsy of the everted, eroded and poorly stained cervix. The discovery of abnormal cells in the vagina by the Papanicolaou smear test is often the first indication that the patient has a carcinoma in situ of the cervix. Graham<sup>11</sup> picked up by vaginal smear 38 unsuspected cervical carcinomas, 28 of which were carcinoma in situ. Of 135 cases of carcinoma in situ reported by Younge et al., 100 were discovered by routine biopsy, 58 in the outpatient clinic and 42 by biopsy at the time of conservative gynecologic surgery. The sites chosen for biopsy are at the junction of the erosion and the normal squamous epithelium usually at 6 and 12 o'clock, or at a site dictated by a positive Schiller test. In Younge's series, in 27 of 29 cases the Schiller test was positive and responsible for the discovery of a curable carcinoma in situ. The Schiller test (Figs. 1 and 2) is dependent upon the difference in staining between normal and abnormal squamous epithelium. The normal squamous cell as it contains glycogen takes the iodine stain and assumes a dark brown color; the columnar epithelium and the connective tissue of an erosion, as they contain no glycogen, fail to stain; the positive Schil-

ler area, if it occurs, is at the border of the erosion and the darkly staining normal squamous epithelium. The noniodine staining squamous epithelium appears normal to the eye. The failure to stain indicates lack of glycogen and is found in carcinoma in situ, leukoplakia or paraneoplasia, or chronic inflammation. Only the pathologist can tell the difference by study of the tissues removed by biopsy. Carcinoma in situ is frequently multicentric in origin and several nonstaining areas may be seen.

If the diagnosis of carcinoma in situ is suggested by vaginal smear or proven by biopsy, the next step is to rule in or out invasive carcinoma of the cervix since carcinoma in situ may be found at the advancing edge of an invasive carcinoma. Biopsy of the cervix under anesthesia with special attention to the endocervical canal is performed as follows. The cervix is gently dilated and tissue is secured from both exo- and endocervix by one of two biopsy methods: (1) cold knife cone or (2) multiple wedge biopsies. The cold knife cone method, if done carefully, will present the pathologist with a complete cone of the cervix, containing both exo- and endocervical tissue. The disadvantage of this method is that the entire cervix is denuded, bleeding may be profuse, control is difficult and delayed bleeding may occur. Multiple wedge biopsies of the anterior, posterior and lateral margins of the cervix allow space for sutures to control the bleeding and result in less scarring and stricture. Each biopsy specimen should be laid out and marked so that the pathologist can identify (1) the epithelial surface, (2) the exocervix, and (3) the endocervix and should preferably be taken to the laboratory by the surgeon. Only by doing so can the pathologist identify the epithelial surface of both exo- and endocervix and decide whether the lesion is carcinoma in

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situ or invasive. A wait for permanent sections is mandatory.

If invasive cancer is ruled out, the treatment is dependent upon the age of the patient and her desire for further children. If young, and desirous of children, conservative management is possible. This consists of surgical excision of all of the carcinoma in situ tissue. The patient is followed up by repeated vaginal smears and cervical biopsies. Pregnancy with delivery through the cervix is not contraindicated and such cases have been reported by Younge et al., Kottmeier and others. The physician accepts the responsibility of prolonged and careful follow-up of his patient with repeated examinations, smears and biopsies. Since the transition from an in situ to an invasive carcinoma probably takes many months to many years, no haste is necessary in the treatment.

The definitive treatment for carcinoma in situ of the cervix in the woman who is through childbearing is total hysterectomy with removal of a cuff of vagina. Since the lesion is multicentric and occasionally involves the vaginal mucous membrane adjacent to the cervix, a Schiller test must be done immediately preceding the operation to demonstrate the spread of the lesion, if present, and to indicate the amount of vagina to be removed. Recurrence of or persistence of carcinoma in situ in the vaginal vault has occurred as long as six to ten years after hysterectomy.<sup>9</sup> All patients are followed post-

operatively by physical examination, Papanicolaou smear and Schiller test at six to 12-month intervals. If a suggestive recurrence is discovered, invasive cancer must again be ruled out and if noninvasive a partial vaginectomy from below is done.

Radiotherapy has found little usefulness in the management of carcinoma in situ since the dosage necessary to eradicate this lesion approaches the dosage used for invasive carcinoma and is apt to be too destructive. Surgical extirpation of the uterus, cervix and a cuff of the vagina is curative. Since this lesion often occurs in younger women, ovarian function can be preserved.

### Cancer of the Cervix

To understand the problems of cancer of the cervix the practitioner must be familiar with the various stages used in describing the extent of the tumor. The accompanying illustration (Fig. 3) demonstrates graphically the various stages. It is easy to remember that Stage I concerns the cervix alone; Stage II, the cervix, upper vagina or slight extension laterally; Stage III, the cancer has spread to the wall of the pelvis or down the length of the vagina; Stage IV involves the bladder or rectum, or both, or has extended distally. Thus, with the illustration and this brief description the meaning of the stages

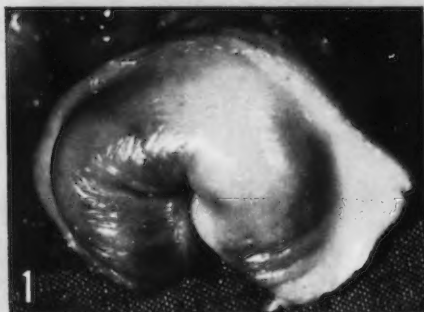


Fig. 1. Schiller's test; cervix uteri before iodine staining: Carcinoma in situ.



Fig. 2. Schiller's test; after iodine staining: Carcinoma in situ.

# CLASSIFICATION OF THE STAGES OF CA

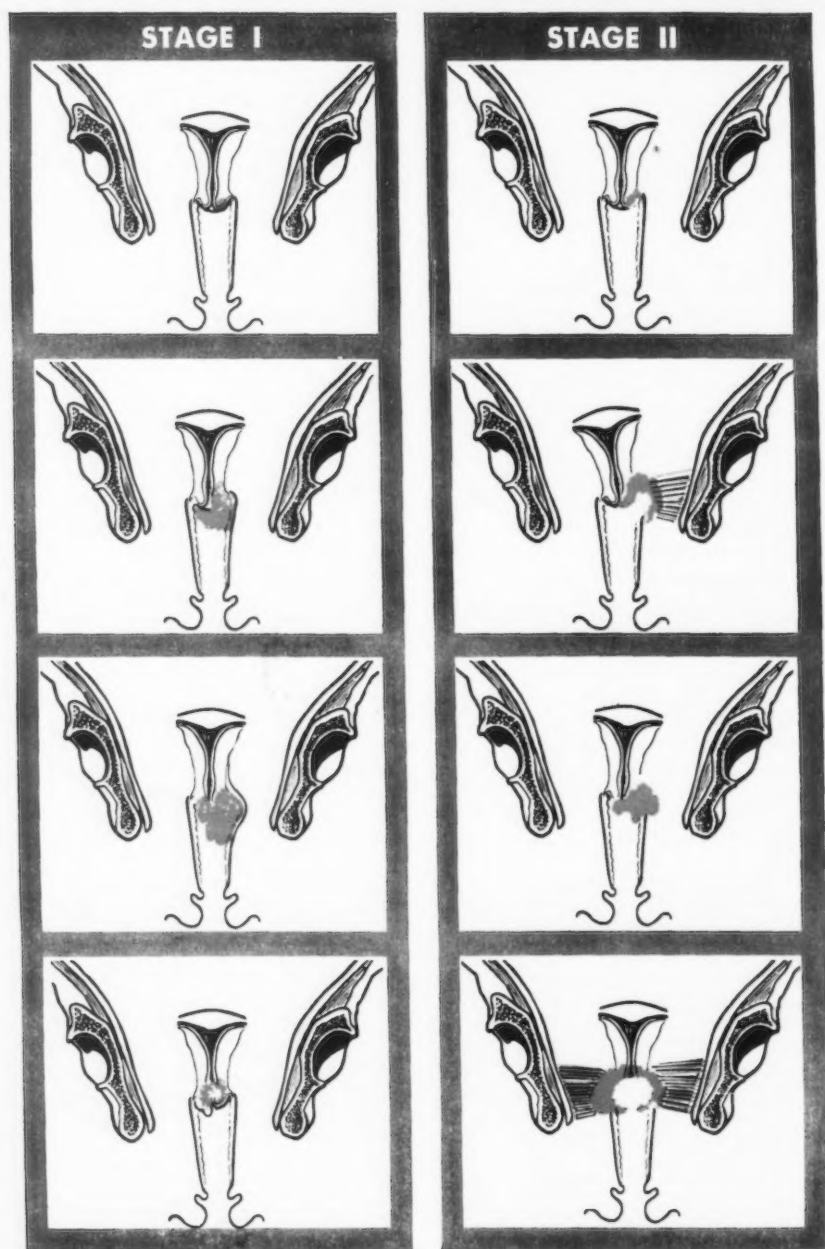
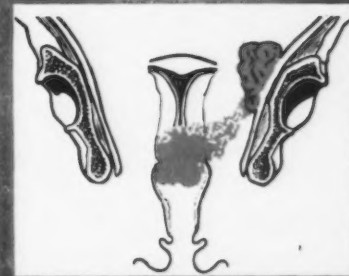
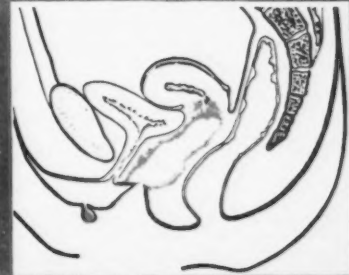
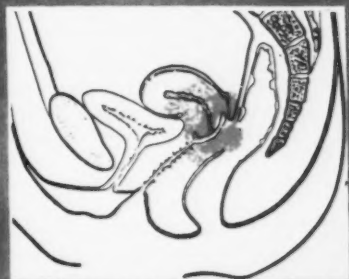
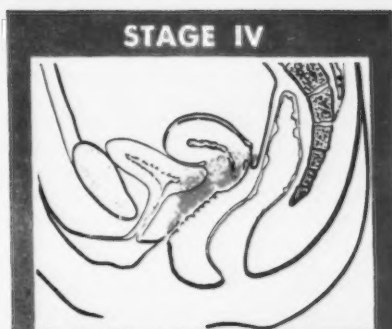
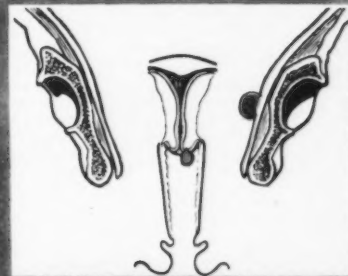
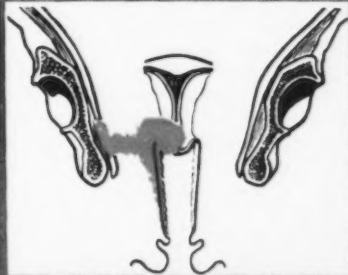


Fig. 3

# OF CARCINOMA OF THE UTERINE CERVIX



should be clearly and easily understood.

The treatment in Stage I can be either surgical or radiologic. Both methods give nearly identical results. In the surgical group the cervix is removed and therefore no recurrence can occur. In the radiologic group some of the cervix remains and therefore there is a slight chance of a regrowth of the tumor. Thus, the surgical treatment may have a slight advantage. It must be remembered that the surgical treatment must be radical, simple total hysterectomy not being sufficient to cure most cases. It must also be remembered that in a certain percentage of cases the surgical operation may be followed by the complication of a ureterovaginal fistula. This may occur in as many as 8 to 10 per cent of the cases. For this reason radiologic treatment may have a slight advantage.

It is accepted in most clinics that there is a difference in the response of certain patients and their tumors to radiation and it may be that certain radiologic failures are due to this phenomenon. To select cases by determining radiation resistance and sensitivity is one of the problems confronting us. It can be done by examination of both the histologic slide following radiation and the vaginal smear following radiation. These methods are not yet available to all; some day they will be but to date they are not. If the surgeon or radiologist, as he gives his divided treatments, is impressed by the lack of response to radiation the case should certainly be turned over to the surgeon for surgical therapy. The surgical treatment must be of the Wertheim hysterectomy type with careful bilateral pelvic lymph node dissection and removal of a large vaginal cuff (Fig. 4). This operation is formidable and should not be tried by one who has not had the opportunity to see the operation done by an expert. It is not easy and the large clinics are receiving more and more patients with recurrence who have been incompletely operated upon. There is actually but one chance to cure cervical cancer whether by surgery or radiation, and this is the first treatment. In cases of early Stage II or Stage II A as it is called, the same results follow radiation and surgical

treatment and again the choice should depend upon the response to radiation. A poor response patient should be operated upon. In Stage II B, the extension may make the surgical attack formidable and some of these patients will be found so advanced that nothing but an exenteration operation will offer a chance of cure by surgery. These cases should be treated with radiation for it offers an equal chance for cure as does surgery without serious complications or need for colostomy or ileal loop. In Stage III, a pelvic exenteration is the only surgical operation that is curative. Radiation therapy can offer a 30 per cent plus chance for cure and this must be judged against perhaps a slightly higher result by means of ultraradical surgery. If the tumor or patient is radiation resistant, surgical treatment is the treatment of choice. In Stage IV the tumor, if it is in the bladder or rectum, is best treated by ultraradical surgery or exenteration. The results by radiation methods are so poor that it is doubtful if radiation should even be suggested. The outlook in patients with distant metastases is so poor that radiation as a palliative measure is best.

In cancers occurring in the cervical stump the same methods of treatment should be observed. In recurrences following the radical surgical operation, either further surgery or radiation should be tried. In three of ten of our surgical failures radiation effected a cure for five years or more. Radiation failures are best treated by surgical treatment, secondary radiation not being very effective.

In the hands of an expert either radiation or surgical operation is usually satisfactory, the surgeon advocating the surgical removal and the radiologist radiation. The choice will be better decided when methods of determining radiation resistance or sensitivity are perfected.

### **Pelvic Exenteration**

Pelvic exenteration has become an accepted curative surgical procedure in the management of extensive and recurrent carcinomas of the cervix uteri. That such radical surgery can ever be curative is due

to the fact that cervical cancer often remains confined to the pelvis. Autopsy studies<sup>2</sup> have demonstrated that 40 to 50 per cent of the patients died with the carcinoma still limited to the pelvis. The favorable results achieved by Meigs<sup>23</sup> and others<sup>6</sup> in the surgical therapy of Stage I and early Stage II cases by radical hysterectomy of the Wertheim type and radical lymphadenectomy led the way to the introduction of the pelvic exenteration operation by Brunschwig<sup>4</sup> in 1948. Three types of exenteration are done dependent upon the extent of the carcinoma. A total pelvic exenteration (Fig. 5) means removal of the uterus, adnexa, lymphatic channels and perivascular lymph nodes, plus the bladder, rectum, vagina and vulva. An anterior exenteration preserves the rectum and is applicable to the cancers that have grown anteriorly. The organs removed are the bladder, uterus, adnexa and vagina and the ureters are implanted into the rectosigmoid as in a total cystectomy. A posterior pelvic exenteration spares the bladder and removes the uterus, adnexa and the rectum because of the posterior extension of the disease.

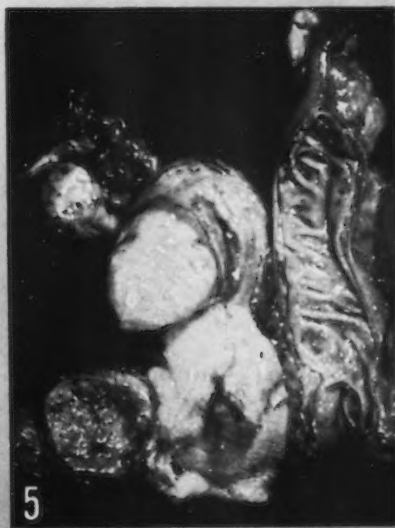
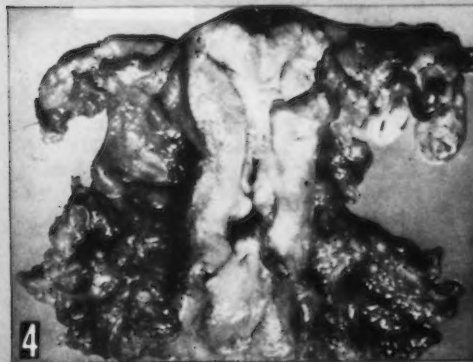
There are three indications for pelvic exenteration. The first indication is failure of irradiation therapy with disease persistent after a full course of x ray and

radium. Usually these radiation resistant cases are apparent at close of their therapy. Occasionally the disease recurs months to years following irradiation and an exenteration is the only chance of cure. These cases are often those in which satisfactory irradiation was not possible due to such complications as infection secondary to an old pelvic inflammatory disease, or distortion of the uterus by fibroids, or some mechanical factor which made radium application difficult. As our experience has increased and cases are individualized, fewer radiation failures are seen on the above-mentioned basis. Resistance to radiation is another factor in the recurrence of tumor.

The second indication for pelvic exenteration is failure of cure of the cervical carcinoma by either total hysterectomy or Wertheim hysterectomy. Total hysterectomy is inadequate treatment for any invasive carcinoma of the cervix. A recurrence which follows total hysterectomy is difficult to treat with radium since adequate and safe irradiation is almost impossible with the uterus gone. In these cases pelvic exenteration offers a reasonable hope of cure if the recurrence is localized to the vaginal vault and adjacent organs. Silva, Friedell and Parsons found it possible to do an exenteration on six such

Fig. 4. Wertheim hysterectomy for carcinoma of cervix.

Fig. 5. Total pelvic exenteration for carcinoma of cervix.



cases. Unfortunately, total hysterectomy is considered by some as adequate therapy for invasive cervical carcinoma.

In an occasional case the recurrence that occurs after a radical hysterectomy and lymphadenectomy is localized and can be removed successfully by pelvic exenteration. These recurrences usually follow radical hysterectomy for Stage II B carcinomas; i.e., those that involve the vagina deeply or invade the paracervical tissue. The five-year survival figure for radical hysterectomy was only 43 per cent in this group in Parsons<sup>31</sup> series as compared to a 79 per cent five-year cure rate in Stage I and II A. If surgery is contemplated in Stage II B cases, both Parsons,<sup>31</sup> and Brunschwig and Daniel<sup>5</sup> recommend anterior or posterior exenteration depending on the direction of the extension of the disease. Four of the 60 cases of pelvic exenteration reported by Parsons<sup>31</sup> followed prior Wertheim hysterectomy.

The third indication for pelvic exenteration is the rare Stage IV lesion which has invaded the bladder or rectum and is still surgically resectable. Irradiation therapy almost invariably results in a fistula and the salvage following radiation in Stage IV carcinomas is very poor.

This major operative procedure is done only if the surgeon finds that he can remove all of the carcinoma. If evidence of distant metastases exists, or there is bony invasion, operation is not attempted. Some cases are explored and the operation abandoned if all the disease cannot be removed, or there are many large and adherent lymph nodes. Pelvic exenteration is rarely done for palliation. In the patient in whom the surgeon has been successful in removing all of the cancer, a comfortable, useful life is possible. Mothers have lived to care for their children; school teachers and secretaries to return to their employment. The major problem has been the diversion of the urinary stream. This has been accomplished by the Bricker ileal loop or the isolated loop of sigmoid as done by Parsons.<sup>25</sup> Both of these techniques avoid the wet colostomy with its foul mixture of urine and feces. The separate openings for urine and feces allow for

the use of the sealed bags for collection of urine, and the usual colostomy management. Late urinary tract complications are avoided by these techniques and the patient can lead an acceptable social existence.

### The Results of Pelvic Exenteration

An analysis of the results of pelvic exenteration demonstrates that the operative mortality ranges between 15 and 20 per cent.<sup>3, 5, 31, 32</sup> Few patients with positive lymph nodes survive for five years. Brunschwig<sup>3</sup> and Ulfelder<sup>32</sup> each report a single case. If the nodes are negative, the outlook is better. In Brunschwig's<sup>5</sup> large series, 12 of 67 patients, or 18 per cent, survived five years. Parsons<sup>31</sup> reports seven of 13 alive and well at five years. Ulfelder<sup>32</sup> gives the results at the Massachusetts General and Pondville Hospitals in years 1948 to 1953 as follows: total number of cases 43; alive and well 5½ to 9½ years later, eight patients—one with positive nodes. These five-year results demonstrate that pelvic exenteration has a reasonable five-year salvage and is one of the rarely applicable, but life-saving surgical procedures.

### Carcinoma of Corpus and Cervix and Endocervix

The accepted classification used in the *Annual Reports on the Results of Treatment in Carcinoma of the Uterus* divides these tumors into three divisions—carcinoma of cervix uteri; carcinoma of corpus uteri; and carcinoma of corpus and endocervix. The third group, carcinoma of corpus and endocervix, is dependent upon carcinoma being found microscopically in both corpus and endocervix.

Since the diagnosis of corpus carcinoma is dependent upon a curettage, the recommended procedure is to do a fractional curettage in order accurately to determine the site of origin and if possible the spread of the disease. The following steps are followed: (1) curettage of the endocervical canal without passing the internal os, (2) dilatation of the cervix, (3) curettage of the lower endometrial



cavity, (4) curettage of the uterine fundus. Specimens removed from the different parts of the uterus are kept separately and each examined microscopically. All cases with carcinoma found in both cervix and corpus are classified as carcinoma of corpus and endocervix. These lesions usually either originate low in the endometrial canal or are such long standing lesions that the exact site of origin is impossible to determine (Figs. 6 and 7). Carcinoma of the corpus is an adenocarcinoma confined to the area of the uterus above the internal os (Fig. 8). This classification replaces the older nomenclature of cancer of the endometrium, or cancer of the fundus. The classification does not include chorionepithelioma, carcinosarcoma or other rare malignant mixed tumors of the uterus. Heyman found that in a series of 952 uterine carcinomas 172 involved both cervix and corpus, an incidence of 18 per cent.

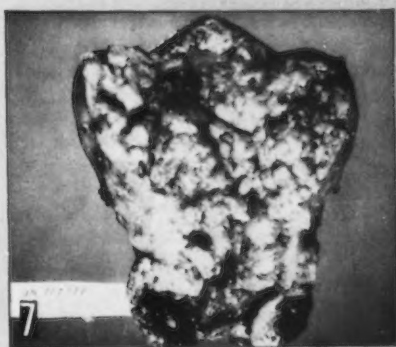
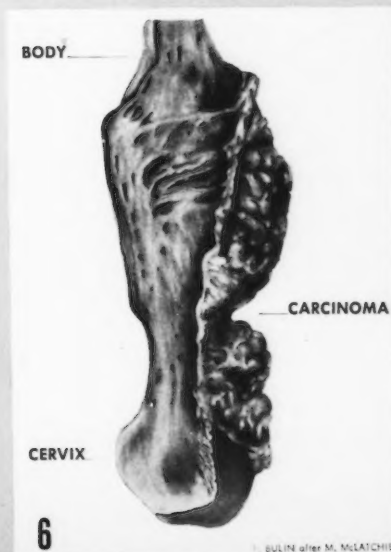
The reason for insisting upon a fractional curettage and separating lesions in-

volving both endocervix and corpus from corpus lesions alone is that the treatment and the prognosis of the two lesions is quite different. Carcinoma of the corpus and endocervix is managed in the same way as carcinoma of the cervix, that is, by either extensive irradiation, or if by surgery, by radical hysterectomy after the Wertheim method, and pelvic lymphadenectomy. Carcinoma of the corpus is a less extensive disease and can be treated by simple total hysterectomy and bilateral salpingo-oophorectomy preceded by intracavitary radium or x-ray treatment. Since simple total hysterectomy is not adequate surgery in invasive carcinoma of the cervix uteri, neither is it adequate in carcinoma of the corpus and endocervix. Metastases to lymph nodes occur more often in lesions of corpus and endocervix. In the series reported by Liu and Meigs, seven of 14 cases of carcinoma of corpus and endocervix subjected to radical hysterectomy and lymphadenectomy had positive lymph nodes, while only four of 33 cases of carci-

Fig. 6. Carcinoma of corpus and endocervix.

Fig. 7. Carcinoma of corpus and endocervix.

Fig. 8. Carcinoma of corpus uteri.



noma of corpus had nodal involvement. The prognosis of these two lesions is quite different. Kottmeier reports from the Radiumhemmet during the years 1936 to 1945 a 60.2 per cent absolute cure rate in carcinoma of the corpus, while during the same period the cure rate of carcinoma of corpus and endocervix was only 32.5 per cent. Graham<sup>10</sup>, reporting on the experience at the Massachusetts General and Pondville Hospitals, records a 57 per cent five-year survival in carcinoma of corpus and only 16 per cent in a small series of carcinoma of corpus and endocervix.

In order to improve the survival rate in carcinoma of the uterus we feel that if fractional curettage demonstrates involvement of corpus and endocervix, treatment should consist either of radium irradiation of the uterus, cervix and vagina and x-ray treatment of the lateral pelvic walls, or radical hysterectomy (Wertheim) with complete removal of uterus, cervix, upper half of vagina and perivaginal tissue and pelvic lymphadenectomy. However, if carcinoma of corpus only is found on fractional curettage, the treatment is determined by two factors, the extent of the disease and the physical state of the patient. The clinical classification of carcinoma of the corpus used in the *Annual Reports on the Results of Treatment in Carcinoma of the Uterus* takes these two factors into consideration as follows:

Stage I. Growth confined to the corpus.

Group A. Patients on whom operation is advisable.

Group B. Poor operative risks.

Stage II. Growth has extended outside of the uterus.

Stage I, Group B and Stage II carcinomas of the corpus should only be treated by radiotherapy unless ultraradical surgery is contemplated. Intracavitary radium in both uterus and vagina is followed by x-ray treatment of the pelvic walls. The results following radiotherapy in Stage I, Group B at Radiumhemmet<sup>10</sup> show a 50.8 per cent five-year survival, in Stage II, 27.5 per cent five-year survival.

The possible methods of treatment of Stage I, Group A patient with carcinoma of the corpus are as follows: (1) Radio-

therapy alone. (2) Total hysterectomy and bilateral salpingo-oophorectomy. (3) Radiotherapy followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. (4) Radical hysterectomy (Wertheim) and pelvic lymphadenectomy.

Radiotherapy by the multiple capsule radium pack method for Stage I, Group A has produced excellent results in the hands of Heyman and Kottmeier; i.e., 62 per cent five-year survival. In this series 13 per cent of the cases treated initially with radium showed signs of recurrence and total hysterectomy was done. Hunt, using x ray and radium in Stage I lesions, achieved a 77.7 per cent five-year survival in a small series. Few sizable series are available for comparison. Certainly the usual tandem method of radium application will not approach these five-year results.

In this country the surgical removal of the entire uterus, tubes and ovaries has produced the best results in the treatment of the Stage I carcinoma of the corpus. Difference of opinion exists as to whether surgery alone or radiotherapy followed by surgery should be used. The majority of gynecologists<sup>1, 7, 20, 24, 27, 29, 30</sup> have favored the preoperative use of some form of radiotherapy. A minority<sup>10, 22</sup> have favored surgery alone. As shown by Corscaden and Tovell, preoperative radium will reduce the size of bulky tumors and facilitate the surgical removal. Arneson presents convincing evidence that preoperative irradiation will double the chances of survival in patients with undifferentiated tumors in a large uterus, i.e., greater than 13 cm. The prognosis for surgical treatment alone is excellent in the patient with a small uterus and a well differentiated tumor. Radiotherapy preoperatively has been successful in diminishing the incidence of vaginal wall recurrences. In our series<sup>10</sup> there were 12 vaginal recurrences in 124 patients treated by surgery alone and four in 89 patients treated by radium followed by surgery. The five-year survival figures achieved by radiotherapy followed by surgery<sup>1, 7, 15, 20, 24, 30</sup> justify the recommendation that this is the treat-

ment of choice. Improvements in anesthesia, chemotherapy, blood replacement and care of the aged which have been shown by McKelvey to increase operability, will increase the five-year survival rate.

### Radical Hysterectomy

Since radical hysterectomy of the Wertheim type combined with pelvic lymphadenectomy has been found to be successful<sup>6, 23</sup> in the treatment of carcinoma of the cervix, an attempt to apply this operation to cancer of the corpus is understandable. Lymph node metastases have been demonstrated to be more common in carcinoma of the corpus<sup>12, 17, 18</sup> than previously suspected. Graham,<sup>10</sup> in a collected series of 228 patients subjected to bilateral lymphadenectomy, noted an incidence of 21 per cent. More extensive surgery also may increase the five-year survivals because of the wider excision and less chance

of local recurrence. However, the applicability of this major operation with its high complication rate is limited by the fact that the patients with carcinoma of the corpus are usually elderly, fat, hypertensive and occasionally diabetic. For this reason a higher operative mortality can be expected. Graham<sup>10</sup> reports 3 per cent or five deaths in 164 operations in series collected from the literature. The results of radical hysterectomy reported by Winteron on 57 cases is as follows: 45 patients or 79 per cent survived five years. Parsons<sup>26</sup> reported an 81 per cent five-year survival in a series of 33 patients. At the present time these figures from small groups of cases are not sufficiently better than the figures for cases treated with radiation followed by hysterectomy to justify the added risks of complications and the increased mortality of the extended procedure.

### References

1. Arneson, A. N.: Evaluation of use of radiation in treatment of endometrial cancer. *Bull. New York Acad. Med.* 29:395-410, 1953.
2. Behney, C. A.: Advanced carcinoma of cervix; with report of 166 necropsies. *Am. J. Obst. & Gynec.* 26:608-614, 1933.
3. Bricker, E. M.: Total exenteration of the pelvic organs. In Meigs, J. V., Ed.: *Surgical Treatment of Cancer of the Cervix*. New York. Grune & Stratton, Inc. 1954; pp. 349-374.
4. Brunschwig, A.: Complete excision of pelvic viscera for advanced carcinoma; one-stage abdominoperineal operation with end colostomy and bilateral ureteral implantation into colon above colostomy. *Cancer* 1:177-183, 1948.
5. Brunschwig, A., and Daniel, W.: Evaluation of pelvic exenteration for advanced cancer of cervix. *Surg., Gynec. & Obst.* 103:337-341, 1956.
6. Carter, F. B.: Radical hysterectomy with bilateral dissection of the pelvic lymph nodes. In Meigs, J. V., Ed.: *Surgical Treatment of Cancer of the Cervix*. New York. Grune & Stratton, Inc. 1954; pp. 139-148.
7. Corscaden, J. A., and Tovell, H. M. M.: Management of carcinoma of corpus. *Am. J. Obst. & Gynec.* 68:737-760, 1954.
8. Galvin, G. A., and TeLinde, R. W.: Present-day status of noninvasive cervical carcinoma. *Am. J. Obst. & Gynec.* 57:15-36, 1949.
9. Graham, J. B.: Recurrent cancer of the cervix following surgery and its treatment. In Meigs, J. V., Ed.: *Surgical Treatment of Cancer of the Cervix*. New York. Grune & Stratton, Inc. 1954; pp. 423-428.
10. Graham, J. B.: Treatment of choice in cancer of the uterine corpus. *New England J. Med.* 254:1112-1119, 1956.
11. Graham, R. M.: The clinical evaluation of the vaginal smear. In Meigs, J. V., and Sturgis, S. H., Eds.: *Progress in Gynecology*. Volume II. New York. Grune & Stratton, Inc. 1950; pp. 133-138.
12. Henriksen, E.: Lymphatic spread of carcinoma of the cervix and of the body of the uterus; study of 420 necropsies. *Am. J. Obst. & Gynec.* 58:924-942, 1949.
13. Hertig, A. T., and Mansell, H.: What is carcinoma in situ of the cervix? In Meigs, J. V., and Sturgis, S. H., Eds.: *Progress in Gynecology*. Volume III. New York. Grune & Stratton, Inc. 1957; pp. 520-534.
14. Heyman, J., Reuterwall, O., and Benner, S.: The radiumhemmet experience with radiotherapy in cancer of the corpus of the uterus; classification, method of treatment and results. *Acta radiol.* 22:11-98, 1941.
15. Hunt, H. B.: Comparative radiotherapeutic results in carcinoma of the endometrium as modified by prior surgery and postirradiation hysterosalpingo-oophorectomy. *Radiology* 66:653-665, 1956.
16. Ingersoll, F. M.: Unpublished data.
17. Ingersoll, F. M., and Meigs, J. V.: Lymph node dissection for carcinoma of the endometrium. In *Proceedings of the Second National Cancer Conference—1952*. New York. American Cancer Society, Inc. 1954; pp. 747-753.
18. Javert, C. T., and Hofmann, K.: Observations on surgical pathology, selective lymphadenectomy, and classification of endometrial adenocarcinoma. *Cancer* 5:485-498, 1952.
19. Kottmeier, H. L.: *Carcinoma of the Female Genitalia*. Baltimore. Williams & Wilkins Co. 1953.
20. Lampe, I.: Combined surgical and radiological treatment for endometrial carcinoma. In *Proceedings of the Second National Cancer Conference—1952*. New York. American Cancer Society, Inc. 1954; pp. 753-764.
21. Liu, W., and Meigs, J. V.: Radical hysterectomy and pelvic lymphadenectomy: review of 473 cases including 244 for primary invasive carcinoma of cervix. *Am. J. Obst. & Gynec.* 69:1-32, 1955.
22. McKelvey, J. L., and Prem, K. A.: Adenocarcinoma of the endometrium. In Meigs, J. V., and Sturgis, S. H., Eds.: *Progress in Gynecology*. Volume III. New York. Grune & Stratton, Inc. 1957; pp. 465-475.

References continued on page 203

# Radiotherapy in Cervical Carcinoma

H.-L. Kottmeier, M.D.

Although carcinoma of the cervix can be successfully treated by radical surgery, the primary treatment of choice is irradiation. The intracavitary application of radium or another gamma-radiating source in suitable applicators of different lengths and sizes is as important in carrying out a satisfactory course of treatment as is external irradiation.

In recent years, some radiotherapists have abandoned intracavitary irradiation in advanced cases of cervical carcinoma after having achieved primary healing of the tumor by administering a dose of 5000 to 7000 r to the total pelvis from external radiation. Although this is valuable from the point of view of protection we believe that intracavitary treatment is of great significance and should not be abandoned. As a matter of fact the increased number of cases of parametrial fibrosis complicated by hydronephrosis reported in recent years is due to an increased dose applied to the parametrium, as a rule, by external irradiation. At the Radiumhemmet we always consider hydronephrosis occurring after irradiation as a sign of recurrent carcinoma. As a rule we apply a dose of 1500 gamma r plus 2000 roentgen r to the lateral pelvic wall in eight to 10 weeks. Since we have tried to increase the dose by external irradiation or intraparametrial injection of  $Au^{198}$ , we have observed a small number of cases of hydronephrosis as a sequela from the radiation.

In radiotherapy we have to consider the reaction of the connective tissue, the condition of which is quite important in the healing process of a carcinoma. Modern physics and techniques have improved our facilities for applying a dose of 5000 r or more to the total pelvis. The administration of such a dose to a large volume of tissue may, however, be disastrous and may lead to irreparable damage. Although it is desirable to try to give a large dose to

the pelvic wall it is necessary to take other facts, in addition to the dosage distribution, into consideration. The cure rate is not directly related to the dosage applied. We know that a large dose—more than 20,000 r—should be given to the cervix but no proof of our knowledge has been furnished that 5000 to 6000 roentgens given in six weeks are required to cure a carcinoma which has extended to the pelvic wall or has given rise to metastases in regional lymph nodes. Experience has shown that the dose required varies from case to case. Radiotherapy in carcinoma of the cervix needs great experience. We do believe that it is important to watch the patient during the course of treatment, to perform repeated examinations including laboratory tests and vaginal smears, and to stop radiotherapy provided the patient is suffering from weakness, anemia, diarrhea or other similar symptoms.

Every radiotherapist is aware of the fact that the pelvic wall is the most common site of recurrences. The desire to increase the dose to the pelvic wall demands a careful planning of the irradiation with regard to the facts mentioned above. German authorities recommend intravaginal cone therapy, so-called *Kleinraumbestrahlung*, or a combined pendulum-convergence roentgen therapy. At the Radiumhemmet we have not been satisfied with any of these techniques. We try to increase the dose to the pelvic wall by applying telecobalt through multiple small, partly overlapping anterior and posterior portals. As a rule, an area of 6 to 8 cm. is covered by 9 portals. The field treated every day has a diameter of 6 cm. The focus-skin distance amounts to 10 cm. We thus avail ourselves of the divergence of the beam from a small cobalt source. A dose of 2000 r is given to each portal. In order to carry out such a treatment a uro-venography is required for showing the details of pelvic anatomy.

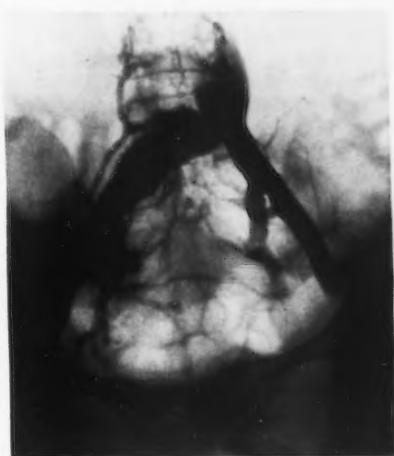
The intracavitary treatment does not

*From Karolinska Sjukhuset, Radiumhemmet, Stockholm, Sweden.*

imply putting some radium into the uterine cavity or the vagina. The treatment should be outlined in close collaboration between a skilled gynecologist and a radiotherapist. The gynecologist should examine the patient under anesthesia, stage the carcinoma and estimate its extension in detail. Cystoscopic and proctoscopic examinations are made. X-ray examination of the lungs and the pelvis, urographic studies and histologic examination of biopsies taken from the growth are required. Urographic information is valuable in planning the treatment. At the Radiumhemmet, hydro-nephrosis or a nonfunctioning kidney has been diagnosed in about 10 per cent of our cases. Such a finding is of importance in outlining the treatment, but it should not influence the staging.

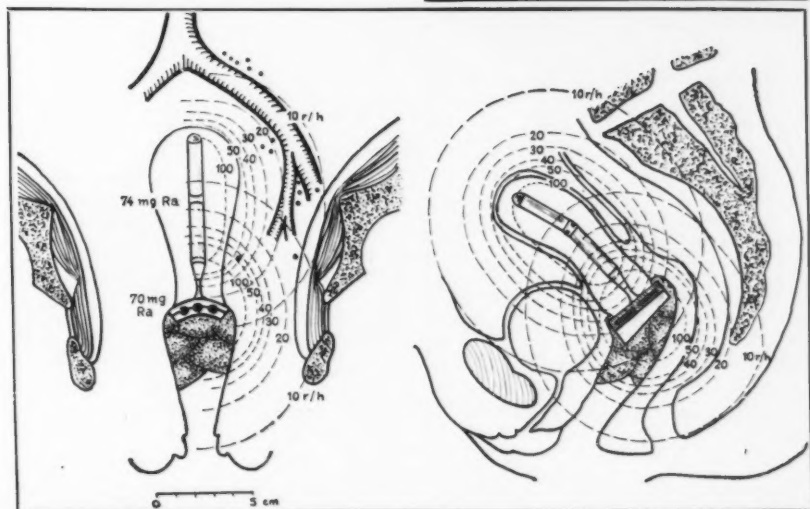
The radiotherapist should distribute the radium into the uterine cavity and the vagina with regard to the clinical findings so that the best possible dosage distribu-

tion is obtained. Different applicators are desirable to render a satisfactory radium treatment possible. The filter is equivalent to 1 mm. Pt. The vaginal applicators should fit well to the growth and the vaginal vaults. The radium in the applicators should be spread out over a large area in order to avoid over-irradiation of the rectum. The applicators chosen, for instance, by Arneson, Corscaden, Ernst or Fletcher are satisfactory for most cases and do not slip as the ovoids sometimes do.



Right—Angiogram showing vascular outline of the pelvis.

Below—Intracavitary radium application (uterine and vaginal) showing dosage distribution of radiation.



The intrauterine radium should be pushed up against the fundus of the corpus in order to prevent a subsequent pyometra. The length of the uterine applicator varies with the length of the cervical canal. As a rule, at the Radiumhemmet, no radium is applied in the lower 2 cm. of the cervical canal in order to avoid over-irradiation of the urinary bladder and rectum.

In planning intracavitary radium treatment many factors should be taken into consideration: the age of the patient, the gross type and extension of the growth, the width of the vagina, the position and size of the uterus and the dosage distribution to the urinary bladder and the rectum. In our experience it is an advantage to read the dose directly in the posterior wall of the bladder and the anterior wall of the rectum. The treatment time is determined from this reading. In this respect the Siemens gammameter has been reliable. The dosage from the intrauterine radium will be considerably increased and that from the vaginal radium will be decreased correspondingly in cases of (1) endocervical carcinoma, (2) spread of the carcinoma to the paracervical tissue in particular, and (3) narrow vagina.

Many different radium methods have been devised. The present Stockholm method is characterized by a fractionated high-intensity technique. In a case of an early carcinoma and a cervical canal 7 cm. of length, we apply 70 mg. of radium both in the uterus and in the vagina for 25 to 35 hours. Three weeks later the application is repeated in the same fashion. The optimal dose is 4000 gamma r in the rectum and 5500 gamma r in the bladder. As far as the optimal dose is concerned, we consider the dose in an area of 2 to 3 cm. and, thus, do not pay attention to the maximum dose in one point. As a rule we do not exceed the dose mentioned in early stages of cervical carcinoma, but in advanced cases we give up to 6000 r from the radium in the anterior wall of the rectum.

I have stressed the importance of individualizing the irradiation and called attention to several factors, but others must

be considered. In infected cases the intrauterine and intravaginal radium should never be employed simultaneously. The adnexa should be excised prior to the irradiation in cases complicated by salpingitis. A rupture of the growth will increase the risk of metastases. The dilatation of the cervical canal is harmless if performed gently.

Radiotherapists often prefer giving external irradiation prior to the application of radium in order to shrink the tumor. Clinical experience and the analysis of vaginal smears on radiation response have convinced us that the intracavitary radium treatment should not be postponed to the day when the full course of external irradiation has been given. As a matter of fact, we like to start radiotherapy by applying radium, provided the external os is easily located.

I have called attention in the preceding paragraphs to the importance of improving the general condition of the patient by various methods. From the radiation point of view, we consider it valuable to let normal tissue recover, as it recovers from radiation more rapidly than does neoplastic tissue. The analysis of vaginal smears taken during the course of radiotherapy is probably of value in outlining a fractionated radiotherapy. At the Radiumhemmet we prefer applying the radium twice with an interval of three weeks.

Although a reliable comparison of therapeutic statistics still is difficult to achieve, a presentation of results obtained on an unselected series of cases is of value provided the cases are divided into the clinical stages internationally agreed upon. The eleventh *Annual Report on the Results of Treatment in Carcinoma of the Uterus* has collected a series of 44,904 patients examined with a view to treatment in the period 1947 through 1951 at 86 institutions. Treatment has been applied in 42,130 patients. The relative five-year recovery rate is: Stage I—70.0 per cent, Stage II—48.6 per cent, Stage III—27.3 per cent and Stage IV—6.7 per cent. The results presented do not represent what actually was achieved by radiotherapy only, as in 5321 of the 42,130 cases. Also



Table I  
CERVICAL CARCINOMA

FIVE-YEAR (1949-1952) APPARENT RECOVERY RATE\*

Stage	No. Pts.	% all Stages	5-yr. Apparent Recovery Rate No.	5-yr. Absolute Survival Rate %	Dead from Intercurrent Disease
I	228	15.7%	201	88.2%	5
II A	401	27.7%	272	67.8%	26
II B	402	27.7%	192	47.8%	12
III	312	21.5%	109	34.9%	4
IV	106	7.3%	8	7.5%	2
I-IV	1449	99.9%	782	54.0%	49
Total	1464†		782	53.4% †	

\*Patients treated at the Radiumhemmet, Stockholm.

†Fifteen patients were not accepted for treatment.

surgery was performed at the time of initial treatment. Besides, surgery was carried out in some cases of radioresistant carcinoma. In the future, the Editorial Committee of the *Annual Report* ardently hopes that it will be possible to agree upon rules for the presentation of statistics on therapeutic results to render a comparison possible.

Table I gives the five-year apparent recovery rate in 1464 cases of carcinoma of the cervix examined with a view to treatment in the period 1949 through 1952 at

the Radiumhemmet. One thousand four hundred and forty-nine cases have received primary radiotherapy in accordance with the present individualized technique. Cases of carcinoma with a deep parametrial involvement fixed to the pelvic wall by a short but not nodular parametrium are staged as II B. Many institutions allot similar cases to Stage III. All cases of cervical carcinoma, diagnosed within the area for which the Radiumhemmet is responsible, are included in the table.

### References continued from p. 199

23. Meigs, J. V.: Radical hysterectomy with bilateral pelvic lymph node dissections; report of 100 patients operated on 5 or more years ago. *Am. J. Obst. & Gynec.* 62: 854-870, 1951.
24. Miller, N. F., and Henderson, C. W.: Corpus carcinoma; study of 322 cases. *Am. J. Obst. & Gynec.* 52:894-903, 1946.
25. Parsons, L.: Total exenteration of the pelvic organs. In Meigs, J. V., Ed.: *Surgical Treatment of Cancer of the Cervix*. New York. Grune & Stratton, Inc. 1954: pp. 322-348.
26. Parsons, L., and Cesare, F.: Wertheim hysterectomy in the treatment of endometrial carcinoma. *Surg., Gynec. & Obst.* 108:582-590, 1959.
27. Payne, F. L.: The role of radiation and of surgery in the management of uterine carcinoma. *Surg., Gynec. & Obst.* 94:715-721, 1952.
28. Pund, E. R.; Nettles, J. B.; Caldwell, J. D., and Nieburgs, H. E.: Preinvasive and invasive carcinoma of the cervix uteri; pathogenesis, detection, differential diagnosis, and pathologic basis for management. *Am. J. Obst. & Gynec.* 55:831-837, 1948.
29. Randall, J. H.; Mirick, D. F., and Wieben, E. E.: Endometrial carcinoma. *Am. J. Obst. & Gynec.* 61: 596-602, 1951.
30. Schmitz, H. E.; Smith, C. J., and Gajewski, C. J.: Effect of preoperative radiation of adenocarcinoma of the endometrium. *Am. J. Obst. & Gynec.* 64:952-970, 1952.
31. Silva, T. F.; Friedell, G. H., and Parsons, L.: Pelvic exenteration for carcinoma of the cervix; clinico-pathological study of sixty operations. *New England J. Med.* 260:519-525, 1959.
32. Ulfelder, H.: Personal communication.
33. Ulfelder, H., and Meigs, J. V.: Surgery of advanced pelvic cancer in women. *New England J. Med.* 246:243-247, 1952.
34. Winterton, W. R.: Discussion on carcinoma of the body of the uterus. *Proc. Roy. Soc. Med.* 47:897-899, 1954.
35. Younge, P. A.; Hertig, A. T., and Armstrong, D.: Study of 135 cases of carcinoma in situ of cervix at Free Hospital for Women. *Am. J. Obst. & Gynec.* 58:867-895, 1949.

# Progress in the Application of Exfoliative Cytology to Cervical Cancer

*John F. W. King, M.D.*

In 1928 Dr. George N. Papanicolaou first described the potential of vaginal exfoliative cytology in the diagnosis of uterine cancer. However, it has only been a little more than ten years since this procedure has been encouraged as a practical laboratory method for the early diagnosis of cervical cancer. In this significant decade, vaginal cytology has been subjected to the scrutiny, criticism and objective evaluation of hundreds of scientists, pathologists and clinicians. Its acceptance has been relatively slow, but its progress has been of the kind that firmly establishes its value, and today it is broadly recognized as one of the most significant cancer control discoveries in half a century.

The American Cancer Society had an early interest in the application of the Papanicolaou technique, but it was not too successful in stimulating early enthusiasm for the procedure while it was being subjected to its necessary ordeal of scientific evaluation. That this testing period was necessary, no one questions, but there are many who believe that the evaluation studies may have been unnecessarily delayed by a reluctance on the part of responsible groups of our profession to give critical assessment to what was a new departure in cancer diagnosis.

The persistent promises evidenced by the work of Dr. Papanicolaou and by a nucleus of his supporters were strengthened in the late forties by reports of pilot cancer detection studies employing the technique, and the Society, as a result of its interest and support of many of these programs, became even more aware of uncovered dividends from the broader application of the vaginal smear.

At approximately the same time, the ex-

panding programs of the National Cancer Institute took rightful recognition of cytology's possibilities, and their activities in supporting and operating significant field studies of cytology in relation to other sites as well as the uterus have been exceedingly important contributions to the fuller use of the technique.

A little more than two years ago, the American Cancer Society, fully aware of the evidence of cytology's particular merit in relation to cervical cancer, set forth and recommended to its sixty incorporated Divisions a ten-point program for the broader application of exfoliative cytology to the earlier diagnosis of cervical cancer. This program was conceived from the experience of the many pilot studies already in operation, and its format was taken from the effective program in Toledo, Ohio, headed by Dr. Edward Burns, and supported by the Academy of Medicine of Toledo and the Lucas County Unit of the American Cancer Society.

The importance of a coordinated professional community effort was recognized and in a two-year period at least 28 Divisions of the American Cancer Society have promoted the formation of cytology coordinating committees with appropriate representation from medical societies, specialty groups and public and professional education interests. The keystone role of the pathologist in the whole program was recognized and the Society attempted in every case to make its appropriate resources available to the recommended program activities of such coordinating committees, but only when these recommendations were endorsed by the component medical societies.

The necessity for increased professional education in cytology was recognized early. Since 1952 the American Cancer Society has given support to the develop-

*Service Section, American Cancer Society, Inc., New York, N. Y.*

ment and growth of the now vital Inter-Society Cytology Council, which brings into conference through its membership many disciplines of interest in cytology, including the research cytologist, the pathologist, the gynecologist, other physicians and cytotechnologists. The Society also has been offering cytology fellowships for many years to physicians in pathology residencies. Since the start of its formal ten-point program, the Society has worked with the College of American Pathologists and the American Society of Clinical Pathologists to promote effective training programs for practicing pathologists, and in the development of standards for the training of cytotechnologists. The recent publication of a brochure for practicing physicians by the ASCP was welcomed by the Society, and the Society has further expressed its professional educational interest in devoting issues of *CA—Bulletin of Cancer Progress* to the importance of cytology and in the development of a monograph on cytology. Last year the American Cancer Society produced the professional education film, "Routine Pelvic Examination and Cytologic Method," and this has been made broadly available throughout the country. In the past two years thirty-five Divisions of the American Cancer Society have reported extensive professional education activity or other support to professional facilities for the application of cytology.

The importance of the cytotechnologist to the effective use of cytology was also early recognized and more than half of the Divisions of the Society offer scholarships for approved training in this special branch of medical technology. Although it is evident that the supply of cytotechnologists currently available is not nearly enough for the potential application of exfoliative cytology, the efforts to stimulate training in this field have significantly reduced the early bottleneck that a totally inadequate number created.

The quality of professional education required in cytology is readily recognized, and the profession knows that the dividends of cytology are realized only when it is in competent, trained hands. When

the American Boards of Pathology made proficiency in cytology a part of its certifying examination requirements, the American Cancer Society correspondingly transferred its fellowship program in cytology to the more appropriate area of its general fellowship program in pathology.

Recently, the California Medical Association passed a resolution recommending to all its membership the importance of including vaginal cytology as part of the periodic physical examination. The Society salutes this action of such a large representative body of the medical profession and looks to the day when every medical society shall do likewise.

The public awareness of the promise of cytology, in some instances, appeared to anticipate the readiness and willingness of the profession to provide the service. The obvious disadvantages of this situation, created with only the best of intent, largely by lay publications, were the confusion and misunderstanding, in the public mind, of the value and purpose of the new technique. The Society in its program, instituted more than two years ago, carefully cautioned against indiscriminate public education before adequate professional services were available. It was further pointed out in properly timed education programs that the vaginal smear was not primarily a diagnostic procedure, but a screening procedure that required professional interpretation for the proper selection of any further diagnostic studies that may be required. Consequently, the technique needed all the safeguards of the usual doctor-patient relationship and it could not be relegated to any "supermarket" variety of application. The importance of regular periodicity in the application of cytology has been emphasized, since it receives its fullest expression in the early diagnosis of cervical cancer when it becomes a regular screening procedure for women over 35 years of age. It has also been suggested that where practical it could be effectively applied to women over 25.

In an effort to achieve proper and effective public education, at least thirty-six of the American Cancer Society's sixty Divi-

sions in the past two years have been carrying out programs that bear the prior endorsement of component medical societies. Suitable printed materials have been made available, and the public education film on cytology, "Time and Two Women," produced early in the Society's basic program has been widely used under professional auspices.

The many discussions on the cost of applying this technique have been carefully considered and the experience of the Society has confirmed the advice of the medical profession generally that such a program can only be ethically and practically carried out on a self-supporting basis. The cost to the patient in a broad variety of programs, within private practice, has

invariably been reasonable, and in view of the potential dividend, it probably represents one of the outstanding bargains in medical service. Needless to say, every self-supporting program with which the Society has been involved has been able to care for any indigent load that has been placed upon it.

With a growing public awareness of vaginal cytology's value, and with properly established services for its proper interpretation, we will realize the full benefits of this significant discovery. The American Cancer Society appreciates the opportunity it has in working with every group of the medical profession in helping to apply this important life-saving procedure in cancer control.

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### Slides for Teaching Exfoliative Cytology

The American Cancer Society has made available for loan through its Divisions a set of 100 teaching slides on *Exfoliative Cytology of the Female Genital Tract*. These slides were developed by Leopold G. Koss, M.D. and Grace R. Durfee, B.S. at the Memorial Center for Cancer and Allied Diseases through a grant from the Harry M. Lasker Memorial Fund.

Sets of these slides have been given to the Cancer Coordinators at each medical school and to the schools approved for training cytotechnicians.

Requests for loan of the set should be addressed to the local State Divisions of the American Cancer Society.

#### Acknowledgment:

Prosthesis shown in Figures 12 and 13 on Page 122 of CA, July-August 1959, was constructed by Dr. Albert Lederman.

# A Statement on Lung Cancer

Dean F. Davies, M.D., Ph.D.

The American Cancer Society entered actively into the war against lung cancer after nationwide publicity had been given to clinical reports of an association between lung cancer and smoking. During the ensuing seven years the Society has been in the forefront of the battle largely through support of research:

To date the American Cancer Society has awarded over 3.4 million dollars in grants for research on lung cancer since 1954.

The large-scale follow-up study carried out by its own staff would have cost an estimated \$10,000,000 without the help of volunteers.

Lung cancer conferences sponsored by the Society were held in: Chocorua, New Hampshire in September, 1952; Prouts Neck, Maine in September, 1953; Atlantic City, New Jersey in February, 1954; Glenburnie, New York in September, 1954; and Princeton, New Jersey in January, 1955.

In March, 1955 an Ad Hoc Research Advisory Committee on Lung Cancer was formed which served the Society, (subsequently as the Advisory Committee on Research on Lung Cancer) until August, 1959.

Under its sponsorship, the First Workshop Conference on Lung Cancer Research was held at Virginia Beach in November, 1957; the Second Workshop Conference on Lung Cancer Research was held at Harri-man, New York, February-March, 1959.

Also under the sponsorship of the Advisory Committee on Research on Lung Cancer a "Cooperative Pilot Study on the Evaluation of Radiologic and Cytologic Screening of a Population for Early Diagnosis of Lung Cancer" was designed and is now in its second year of operation in six Veterans Administration Centers through cooperation of the V. A. Central Office.

In June, 1956 a Study Group on Smoking and Health was formed under the joint sponsorship of the American Cancer Society, American Heart Association, National Cancer Institute and National Heart Institute. Its report was quoted widely in the press in March, 1957 and published in *Science* 125:1129-1133, June 7, 1957.

Subsequently the Board of Directors formed an Ad Hoc Committee on Smoking and Health which was superseded in June, 1959 by the present Committee on Tobacco and Cancer.

The following authorities, agencies or specially appointed advisory groups have studied the problem independently and have made statements indicating their conclusion that cigarette smoking is usually related to lung cancer:

1. Public Health Cancer Association
2. Study Group on Smoking and Health
3. British Medical Research Council
4. Surgeon General of the U.S.P.H.S., Leroy Burney
5. Swedish Medical Research Council
6. Subcommittee on Tobacco and Air Pollution, International Union Against Cancer
7. Herman E. Hilleboe, Commissioner, New York State Health Department
8. Malcolm Merrill, Director, California State Department of Public Health

The evidence which has accumulated on cigarette smoking and lung cancer largely over the last decade is summarized below in five categories:

## Epidemiologic Evidence

After nine studies were published showing an increased incidence of smoking history among lung cancer patients, the American Cancer Society in 1952 began a study of smokers and nonsmokers to discover any differences in subsequent death rates from various causes. At approximately the same time two other follow-up studies were begun, one on physicians in England and the other on a group of veterans of military service in the United States. Results of these three studies have since been published and show remarkable agreement: the incidence of lung cancer is between nine and ten times as high among cigarette smokers as among nonsmokers. While these results were being obtained, about fifteen additional studies on lung cancer patients showed a history of smoking to be associated with the disease. No one has suggested a basis whereby all of these positive correlations could be in error. Nevertheless, such "statistical" evidence alone is insufficient to establish a causal relationship.

## **Chemical Evidence**

Fifteen carcinogenic agents, of which fourteen are polycyclic hydrocarbons, have been reported to be present in cigarette smoke condensate. The other agent is arsenic which is known to be carcinogenic for human skin. Two of the other compounds have produced epidermoid lung cancers in the mouse, rat and hamster.

In addition to the carcinogens, cigarette smoke condensate is made up of a host of compounds of which the major one is nicotine. Of the pharmacologic effects of nicotine, one leads to slowing of ciliary action in the tracheobronchial tree and another is vascular and bronchial constriction through release of adrenaline. Both these effects tend to decrease the efficiency of removal of foreign substances from the respiratory tract.

## **Biologic Evidence**

Tobacco smoke condensates have produced cancers on the skin of mice and rabbits. Lesions resembling cancer or carcinoma *in situ* have been reported in tissue cultures, on the mouse cervix, and on dog and mouse bronchial epithelium after exposure to tobacco smoke or its condensate.

## **Pathologic Evidence**

The tracheobronchial trees of smokers and nonsmokers have been histologically examined extensively at autopsy. The severity of pathologic epithelial changes including metaplasia and carcinoma *in situ* increased as the history of smoking increased. Invasive lung cancer was found only among smokers.

## **Quantitative Relationships**

Examinations of numerous reports of lung cancer indicate that about 15 per cent are adenocarcinomatous and bronchiolar types not believed to be of environmental origin. Smoking does not account for all the remainder. Best estimates indicate that urban factors (probably atmospheric pollution and occupational haz-

ards) could account for 10 or 15 per cent of the total. Cigarette smoking, then, is associated with well over half the cases of lung cancer in the country. Of the remainder, there is no evidence that environmental causes are significantly involved in 15 per cent.

It has been estimated that one of ten smokers will eventually die of lung cancer. The probability of getting the disease is greater the more one smokes. The habit has been compared with the game of Russian roulette. The analogy may be deceiving to the player. Lung cancer accounts for only about 15 per cent of the total increased mortality rate of smokers. If a lung cancer bullet takes up one cylinder it seems likely from the evidence that some of the others are loaded with other diseases.

The possibility exists that factors of resistance operate in some whose natural life expectancy is not shortened by smoking. It is also not unlikely that factors of susceptibility and other external influences operate with cigarette smoking in producing lung cancer. Smokers do tend to differ from nonsmokers in several respects when compared in sufficiently large numbers, but these differences cannot account for to nine-to ten-fold excess of lung cancer deaths among smokers.

Despite the accumulated evidence, it is of course true that there is no mathematical proof that cigarette smoking causes lung cancer. However, decisions in the public interest must be made by agencies and individuals responsible for public health on the basis of the available evidence. The American Cancer Society considers the facts adequate and concludes that CIGARETTE SMOKING IS THE MAJOR CAUSATIVE FACTOR IN LUNG CANCER.

This disease offers a greater opportunity for cancer prevention than any other type of cancer. The discoveries of the last decade in lung cancer research represent a breakthrough in the truest sense. The fringe benefits to be derived from applications of this new knowledge in terms of prevention of death from other diseases may well exceed the potential gains in lung cancer prevention.







# COMING MEDICAL MEETINGS

<i><b>Date 1959</b></i>	<i><b>Meeting</b></i>	<i><b>City</b></i>
Nov. 16-19	Southern Medical Association	Atlanta
Nov. 19-21	Inter-Society Cytology Council	Detroit
Nov. 19-21	Western Surgical Association	Colorado Springs
Nov. 22	Seventh Annual Cancer Seminar, New Jersey Division, American Cancer Society, Inc.	Newark
Nov. 22-26	Puerto Rico Medical Association	Santurce, P. R.
Dec. 11-12	New York Heart Association	New York City
 <i><b>1960</b></i>		
Jan. 9	Northwest Society for Clinical Research	Seattle
Jan. 21-23	American College of Surgeons	Louisville, Ky.
Jan. 28-30	Western Association of Physicians	Carmel, Calif.
Jan. 28-30	Western Society for Clinical Research	Carmel-by-the-Sea, Calif.
Feb. 3-6	American College of Radiology	New Orleans
Feb. 10-12	American Academy of Occupational Medicine	Williamsburg, Va.
Feb. 11-13	Society of University Surgeons	Minneapolis
Feb. 18-20	Central Surgical Association	Chicago
Feb. 21-24	California Medical Association	Los Angeles
Feb. 25-27	Symposium on Fundamental Cancer Research (14th)	Houston
Feb. 29-Mar. 3	American College of Surgeons	Boston

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